REMARKS

I. Status of the Claims

Claims 32-35, 38-39, 42-50, and 59-64 are currently pending. Claims 36-37, 40-41, 51-58 were previously canceled without prejudice, claims 33, 39, and 44 are canceled herein without prejudice.

Claims 32, 38, 42, 45, 47, and 59, i.e., all of the independent claims, have been amended to recite that the pharmaceutical composition is not a health supplement. Support for those amendments can be found in the as-filed specification, for example at page 1, lines 8-9, page 14, lines 20-21, lines 31-33, page 15, lines 1-2, lines 7-8, which differentiate between a health supplement and a pharmaceutical composition.

Dependent claims 62-64 have been added herein. Support for those claims can be found, for example, in Figure 2 and Table 5 of Example 6.

Accordingly, no new matter has been added.

II. Rejections Under 35 U.S.C. § 112, 1st Paragraph

Rejection of Claims 32-58

Claims 32, 34, 35, 38, 42, 43, 45-50, and 59-61 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Office Action at 2. The Examiner asserts that "[t]here was never a question of whether or not applicant was in [*sic,* possession] of the pharmaceutical composition." *Id.* at 3. However, the Examiner asserts that "the written description for the 'pharmaceutically effective concentration to therapeutically treat hyperglyceridaemia' is not present." *Id.*

Applicants respectfully assert that compliance with the written description requirement ***only*** requires that the specification disclose information sufficient to show

that the inventor possessed the invention at the time of the original disclosure. M.P.E.P. § 2163.02. All that is required is that there be a disclosure that "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (citation omitted).

Here, the specification at page 15, lines 6-11 (emphasis added) expressly states that "[i]n [a] more preferred embodiment of the invention, the **pharmaceutical** and/or health supplement **comprises at least one of EPA/DHA ethyl esters and is intended for** a range of potential therapeutic applications including; **treatment of hypertriglyceridaemia**...." And the Examiner has admitted that that was sufficient to allow persons of ordinary skill in the art to recognize that the inventors had possession of a pharmaceutical composition. Such a composition would, at least inherently, necessarily, and inevitably ***require*** a concentration of active ingredient that was pharmaceutically effective concentration to therapeutically treat hyperglyceridaemia. M.P.E.P. 2163.07(a).

Again, the Examiner is respectfully reminded that she has the initial burden of presenting, by a preponderance of evidence, why a person skilled in the art would not recognize in Applicants' disclosure a description of the inventions defined by the claims. M.P.E.P. 2163.04.

For at least the foregoing reasons, Applicants respectfully request withdrawal of this rejection.

Claims 32, 34, 35-38, 43, and 47-50 require a concentration of brominated flame retardants of less than 0.2 µg/kg as measured by the concentration of BDE 47. Example 6, Table 5 on page 30, shows a composition containing "<0.2" µg/kg of BDE 47 after distillation. Accordingly, Applicants assert that there is sufficient written description to support the claimed numerical range. Similarly, new claim 64 recites a pharmaceutical composition wherein the concentration of BDE 47 in the marine oil is less than 5.3 pg/g. Example 6, Table 5, also shows that the composition containing <0.2 µg/kg of BDE 47 after distillation initially contained 5.3 pg/g of BDE 47 before treatment. Accordingly, there is sufficient written description to support the claimed numerical range of "less than 5.3 pg/g" in new claim 64.

Claim 34 recites that "the sum of PCDDs and PCDFs in the marine oil is less than 4.65 pg/g," while new claim 62 recites that "the sum of PCDDs and PCDFs in the marine oil is 0.46 pg/g or between 0.46 and 4.65 pg/g." Figure 2 shows that the sum of PCDDs and PCDFs before stripping was 4.65 pg/g, while after stripping, that sum was less than 4.65 pg/g, i.e., 0.46 pg/g. Similarly, claims 35, 38, 46, and 50 recite that "the sum of TE-PCB in the marine oil is less than 22.6 pg/g," while new claim 63 recites that "the sum of TE-PCB in the marine oil is 0.09 pg/g or between 0.09 pg/g and 22.6 pg/g." Figure 2 shows that the sum of TE-PCB before stripping was 22.6 pg/g, while after stripping, that sum was less than 22.6 pg/g, i.e., 0.09 pg/g. Claims 59-60 recite that the concentration of BDE 47 in the marine oil is less than 12.2 pg/g. Figure 2 shows that the concentration of BDE 47 (2,2',4,4'-TetBDE, IUPAC No. 47) before stripping was 12.2 pg/g, while after stripping, that concentration is less than 12.2 pg/g, i.e., 0.58 pg/g.

The Examiner asserts that, in *In re Weirtheim,* a range was lifted out of an actual range. However, the end point for the range in that case was based on an example's recitation of a specific concentration. In particular, the specification disclosed a range of "25%-60%." An example disclosed a specific concentration of 36%. Their combination was held to provide adequate written description support for a range of "between 35% and 60%," despite the fact that "35%" was not recited in the application.

Here, Applicants are using an example as shown in Figure 2, which recites specific, initial concentrations (a sum of PCDDs and PCDFs of 4.65 pg/g, a sum of TE-PCB of 22.6 pg/g, and a concentration of BDE 47 of 12.2 pg/g), as the bases for "lifting out" ranges using those points as in *Weirtheim*-- as the basis for the claimed ranges, i.e., less than 4.65 pg/g, less than 22.6 pg/g, and less than 12.2 pg/g, respectively. Accordingly, the present situation is analogous to that in *Weirtheim* and, as in that case, sufficient support for the claim limitations is present. Applicants respectfully request withdrawal of this rejection.

III. Rejections Under 35 U.S.C. § 102(b)

Rejections Over EPAX Product Specifications

Claims 32-35, 38, 39, 42-46, 60 and 61 have been rejected under 35 U.S.C. § 102(b) as being anticipated by the product specifications for EPAX 4020EE, 5500EE, 6000EE, or 6010EE. Office Action at 4. Applicants respectfully traverse this rejection.

To anticipate a claim, a single reference must teach either explicitly or inherently each and every element of the claim. M.P.E.P. § 2131. Here, the product

specifications for EPAX 4020EE, 5500EE, 6000EE, or 6010EE fail to teach each and every element of the present claims.

For example, the product specifications do not disclose the concentration of brominated flame retardants as measured by the concentration of BDE 47 in the EPAX products. For at least that reason, the present rejection should be withdrawn.

As a further example, the claims recite a pharmaceutical composition that is not a health supplement. The present specification, at page 21, lines 1-4, defines the term "health supplement" to "include food and food supplement to animals and/or humans, fortification of food, dietary supplement, functional (and medical) food and nutrient supplement." The EPAX products are, thus, health supplements and are excluded from the scope of the present claims. For that additional reason alone, the present rejection should be withdrawn.

Although the FDA does not regulate dietary supplements, which are foods, not drugs (*see, e.g.,* Omacor® vs. Dietary Supplement Omega-3, attached hereto), the FDA has issued qualified health claims for dietary supplements containing omega-3 fatty acids in 2000 and for conventional foods containing the same in 2004 (*see., e.g.,* FDA news dated September 8, 2004, attached hereto). Therein, the FDA expressly recommended that "consumers not exceed more than a total of 3 grams per day of EPA and DHA omega-3 fatty acids, with **no more than 2 grams per day from a dietary supplement**." *Id.* (emphasis added).

In contrast, the FDA has approved the use of 4 grams per day of Omacor® (now called Lovaza™) as a drug, to be used as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride (TG) levels in adult patients. *See* FDA-approved label for Omacor®,

attached hereto. Thus, in contrast to the EPAX products, Lovaza™ is deemed, at least by the FDA, to be a pharmaceutical composition comprising a marine oil which comprises eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in a pharmaceutically effective concentration to therapeutically treat hypertriglyceridaemia.

Finally, as previously discussed, the EPAX products do not comprise a marine oil which comprises eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in a pharmaceutically effective concentration to therapeutically treat hypertriglyceridaemia, as required by all of the pending claims. The study discussed in the Bryhn article (already of record) compared the uptake and effect of three compositions on subjects with relatively low triglyceride levels on their lipid profiles[1]. Each of the three compositions tested comprised EPA ethyl ester and DHA ethyl ester in the same ratio (approximately 1.0 : 0.8) but the concentration of those esters in the compositions differed, as shown below:

EPA EE + DHA EE	Total Omega-3 EE
62.5%	71%
80%	88.5%
85%	93.5%

Despite the different concentrations of fatty acid esters, by administering different volumes of each of the three compositions, subjects received the same amount (5.1 g) of EPA ethyl ester and DHA ethyl ester per day.

In the article, the authors state:

> Concentrated omega-3 fatty acid formulations are very effective in lowering TGs. Even in subjects with essentially normal triglyceride values at study entry (approximately 130 mg/dl), the 85% and the 80%

[1] The effect parameters in this study were the blood lipid fractions for TGs and cholesterol.

> EPA/DHA concentrations lowered TGs by about 15%. **In contrast, the 62.5% concentration had little effect on TGs.** Even though the subjects in the 62.5% treatment group had somewhat higher baseline triglyceride levels (approximately 150 mg/dl), **this concentration, with the same omega-3 fatty acid content as the 85% and 80% concentrations, did not produce a meaningful impact on the triglyceride level.**

Bryhn article (already of record) at page 22 (emphasis added).

Based on those results, it can be concluded that the EPAX products do not comprise a marine oil which comprises EPA ethyl ester and DHA ethyl ester in a concentration that is pharmaceutically effective to therapeutically treat hypertriglyceridaemia. The pharmaceutical effectiveness of those results are supported by the specification for Omacor™ (Lovaza™) in the European Pharmacopoeia 5.3, a copy of which was previously submitted herewith for the Examiner's convenience. That reference indicates that EPA and DHA must be present in a minimum concentration of 80%. *See* European Pharmacopoeia at p. 2. That limit is well above those of the EPAX ***health supplements***. For at least these reasons, none of the EPAX products or their specifications anticipate the present claims. Therefore, for at least these reasons, the rejection should be withdrawn.

Rejection Over Dam

Claims 47-50 and 59 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Dam et al., "Efficacy of Concentrated n-3 Fatty Acids in Hypertriglyceridaemia: A Comparison with Gemfibrozil," *Clin. Drug Invest.* (2001) 21(3):175-181 ("Dam"). Office Action at 3. Applicants respectfully traverse this restriction.

Dam reports the results of a study comparing Omacor and Gemfibrozil in patients with hypertriglyceridaemia. The undated description of Lovaza™ merely recites that "LOVAZA uses a 5-step refinement process that helps to eliminate worries about cholesterol, saturated and oxidized fatty acids as well as worries about environmental toxins ... such as mercury and PCBs." Thus, the description does **not** claim that those components are eliminated, but rather only that the process "helps to" eliminate "worries about" them.

Furthermore, the diagram on the second page of the Lovaza™ information merely states in broad, general terms the components removed during the "early," "secondary," and "late" purification steps. No particular mention is made of any actual process step (e.g., molecular distillation) nor does the description mention any concentrations of any particular pollutants, let alone concentrations of brominated flame retardants, PCDDs and PCDFs, and TE-PCB, as recited in the present claims.

Because Dam and the description of Lovaza™ are wholly silent with respect to the concentrations in the Omacor used in Dam of the particular pollutants (brominated flame retardants, PCDDs and PCDFs, and TE-PCB) recited in the present claims or any methods of obtaining such concentrations, Dam fails to teach each and every claim limitation of the present claims and also fails to provide an enabling disclosure regarding pollutant levels or methods for lowering those pollutants. For at least the reasons presented herein, Dam does not anticipate the present claims. Accordingly, the rejection should be withdrawn.

IV. Conclusion

In view of the amendments and remarks above, Applicants the timely allowance of the pending claims.

Please grant any extension of time required to enter this response and Information Disclosure Statement and charge any additional required fees to our Deposit Account No. 06-916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: September 16, 2008

By: _____
Jill K. MacAlpine
Reg. No. 60,475

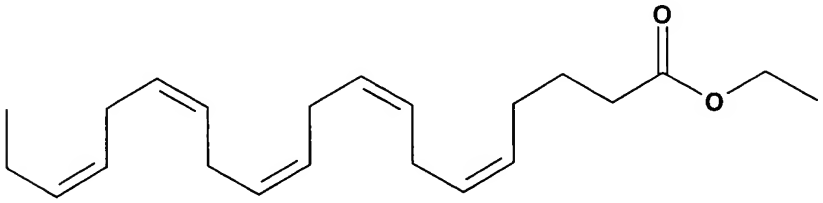
Attachments:

1. Omacor® vs. Dietary Supplement Omega-3
2. FDA news dated September 8, 2004
3. FDA-approved label for Omacor®

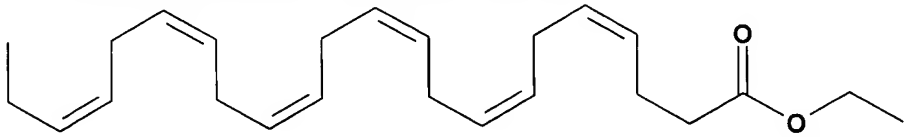
OMACOR®
Omega-3-acid ethyl esters, capsules
Rx only

DESCRIPTION

Omacor®, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each one gram capsule of Omacor® (omega-3 acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).
The structural formula of EPA ethyl ester is:



The empirical formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51.
The structural formula of DHA ethyl ester is:



The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55.
Omacor® capsules also contain the following inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of Omacor® is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase and increased peroxisomal β-oxidation in the liver. Omacor® may reduce the synthesis of triglycerides (TGs) in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

Pharmacokinetic and Bioavailability Studies

In healthy volunteers and in patients with hypertriglyceridemia (HTG), EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (Omacor®) induced significant, dose–dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters. Uptake of EPA and DHA into serum phospholipids in subjects treated with Omacor® was independent of age (<49 years vs. ≥49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on Omacor® in children are not available.

Drug Interactions

Cytochrome P450-Dependent Monooxygenase Activities

The effect of a mixture of free fatty acids (FFA), EPA/DHA and their FFA-albumin conjugate on cytochrome P450-dependent monooxygenase activities was assessed in human liver microsomes. At the 23 μM concentration, FFA resulted in a less than 32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At the 23 μM concentration, the FFA-albumin conjugate resulted in a less than 20% inhibition of CYP2A6, 2C19, 2D6, and 3A, with a 68% inhibition being seen for CYP2E1. Since the free forms of the EPA and DHA are undetectable in the circulation (<1 μM), clinically significant drug-drug interactions due to inhibition of P450 mediated metabolism EPA/DHA combinations are not expected in humans.

CLINICAL STUDIES

The effects of Omacor® 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (42 on Omacor®, 42 on placebo) with very high triglyceride levels (Table 1). Patients whose baseline triglyceride levels were between 500 and 2000 mg/dL were enrolled in these two studies of 6 and 16 weeks duration. The median triglyceride and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.

Table 1. Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (≥ 500 mg/dL)

	TG		LDL-C		CHOL		HDL-C		VLDL-C		non-HDL-C	
	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg
Placebo	788	+6.7	108	-4.8	314	-1.7	24	0.0	175	-0.9	292	-3.6
Omacor 4g/day	816	-44.9	89	+44.5	296	-9.7	22	+9.1	175	-41.7	271	-13.8
Difference		-51.6		+49.3		-8.0		+9.1		-40.8		-10.2

BL = Baseline (mg/dL); % Chg = Percent Change from Baseline; Difference = Omacor - Placebo

Omacor® 4 g per day reduced median TG, VLDL-C, and non HDL-C levels and increased median HDL-C from baseline relative to placebo. Omacor® treatment to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals. Patients should be monitored to ensure that the LDL-C level does not increase excessively.

The effect of Omacor® on the risk of pancreatitis in patients with very high TG levels has not been evaluated. The effect of Omacor® on cardiovascular mortality and morbidity in patients with very high TG levels has not been determined.

INDICATIONS AND USAGE

Omacor® is indicated as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride (TG) levels in adult patients.

Usage Considerations

According to accepted clinical guidelines, excess body weight and excess alcohol intake may be important factors in hypertriglyceridemia (HTG) and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy for HTG.

The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet. (See PRECAUTIONS).

CONTRAINDICATIONS

Omacor® is contraindicated in patients who exhibit hypersensitivity to any component of this medication.

PRECAUTIONS

General

Initial Therapy

Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Omacor® therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG–lowering drug therapy.

Continued Therapy

Laboratory studies should be performed periodically to measure the patient's TG levels during Omacor® therapy. Omacor® therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.

Information for Patients

Omacor® should be used with caution in patients with known sensitivity or allergy to fish.

Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.

Laboratory Tests

In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Omacor® therapy.

In some patients, Omacor® increased low-density lipoprotein cholesterol (LDL-C) levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Omacor® therapy.

Drug Interactions

Anticoagulants

Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Omacor® and concomitant anticoagulants. Patients receiving treatment with both Omacor® and anticoagulants should be monitored periodically.

Cytochrome P450-Dependent Monooxygenase Activities

Omega-3-fatty acid containing products have shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of Omacor® to induce P450 activities in humans has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 g/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation and lactation. No adverse effect on fertility was observed at 2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. It is unknown whether Omacor® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Omacor® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/day based on a body surface area comparison.

In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).
In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation day 6 thorough 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rats given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3000mg/kg/day (7 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rabbits given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Nursing Mothers

It is not known whether omega-3-acid ethyl esters are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Omacor is administered to a woman who is breastfeeding.

Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric Use

A limited number of patients over 65 years of age were enrolled in the clinical studies. In the pooled analyses, safety and efficacy findings in subjects over 60 years of age (approximately 25% of the study population) did not appear to differ from those of subjects less than 60 years of age.

ADVERSE REACTIONS

Treatment-emergent adverse events reported in at least 1% of patients treated with Omacor® 4 g per day or placebo during 8 randomized, placebo-controlled, double-blind, parallel-group studies for HTG are listed in Table 2. Adverse events led to discontinuation of treatment in 3.5% of patients treated with Omacor® and 2.6% of patients treated with placebo.

Table 2. Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel–Group Studies for Hypertriglyceridemia That Used Omacor® 4 g per Day

BODY SYSTEM Adverse Event	Omacor® (N = 226)		Placebo* (N = 228)	
	n	%	n	%
Subjects with at least 1 adverse event	80	35.4	63	27.6
Body as a whole				
Back pain	5	2.2	3	1.3
Flu syndrome	8	3.5	3	1.3
Infection	10	4.4	5	2.2
Pain	4	1.8	3	1.3
Cardiovascular				
Angina pectoris	3	1.3	2	0.9
Digestive				
Dyspepsia	7	3.1	6	2.6
Eructation	11	4.9	5	2.2
Skin				
Rash	4	1.8	1	0.4
Special senses				
Taste perversion	6	2.7	0	0.0

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term.

* Placebo was corn oil for all studies.

Additional adverse events reported by 1 or more patients from 22 clinical studies for HTG are listed below:

BODY AS A WHOLE: enlarged abdomen, asthenia, body odor, chest pain, chills, suicide, fever, generalized edema, fungal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, sudden death, and viral infection.

CARDIOVASCULAR SYSTEM: arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, peripheral vascular disorder, syncope, and tachycardia.

DIGESTIVE SYSTEM: anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, intestinal obstruction, melena, pancreatitis, tenesmus, and vomiting.

HEMATOLOGIC-LYMPHATIC SYSTEM: lymphadenopathy.

METABOLIC AND NUTRITIONAL DISORDERS: edema, hyperglycemia, increased ALT, and increased AST.

MUSCULOSKELETAL SYSTEM: arthralgia, arthritis, myalgia, pathological fracture, and tendon disorder.

NERVOUS SYSTEM: central nervous system neoplasia, depression, dizziness, emotional lability, facial paralysis, insomnia, vasodilatation, and vertigo.

RESPIRATORY SYSTEM: asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, rhinitis, and sinusitis.

SKIN: alopecia, eczema, pruritis, and sweating.
SPECIAL SENSES: cataract.
UROGENITAL SYSTEM: cervix disorder, endometrial carcinoma, epididymitis, and impotence.

DRUG ABUSE AND DEPENDENCE

Omacor® does not have any known drug abuse or withdrawal effects.

OVERDOSAGE

In the event of an overdose, the patient should be treated symptomatically, and general supportive care measures instituted, as required.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving Omacor®, and should continue this diet during treatment with Omacor®. In clinical studies, Omacor® was administered with meals.

The daily dose of Omacor® is 4 g per day. The daily dose may be taken as a single 4-g dose (4 capsules) or as two 2-g doses (2 capsules given twice daily).

HOW SUPPLIED

Omacor® (omega-3-acid ethyl esters) capsules are supplied as 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation OMACOR in bottles of 120 (NDC 0074-5792-01).

Recommended Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Do not freeze.

Keep out of reach of children.

Distributed by Ross Products Division, Abbott Laboratories, Columbus, OH 43215, USA.

Black
Pantone Violet
PMS 1245
Non-varnish area inside
Label Size: 6.3" x 4"

NDC 65726-424-27

Omacor®
(omega-3-acid ethyl esters) Capsules

Each capsule contains 1 gram omega-3-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.

Each capsule provides:
Eicosapentaenoic acid (EPA) ethyl ester: 465 mg
Docosahexaenoic acid (DHA) ethyl ester: 375 mg

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].
Do not freeze.

See package insert for complete prescribing information.

Rx only

120 Capsules

Reliant PHARMACEUTICALS, INC.

Manufactured for:
Reliant Pharmaceuticals, Inc.
Liberty Corner, NJ 07938
by:
Cardinal Health
St. Petersburg, FL 33716

2742M400

N 3 65726 42427 2

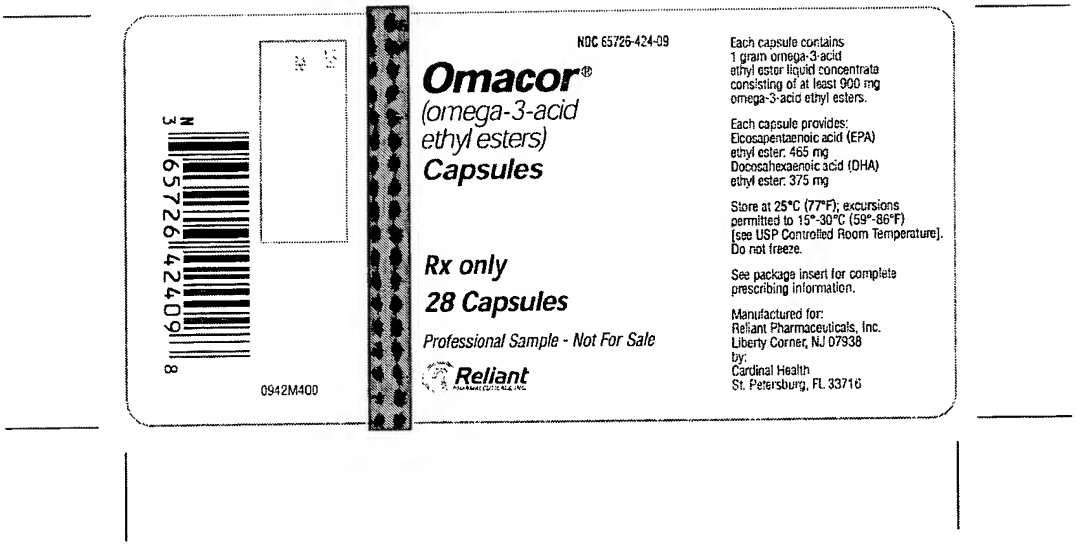
Black

Pantone Violet

PMS 1245

Non-varnish area inside

Label Size: 4.3" x 2.125"



Black
Pantone Violet
PMS 1245
Non-varnish area inside
Label Size: 6.3" x 4"

LOT
EXP

2742M400

N 3 65726 42427 2

NDC 65726-424-27

Omacor®
(omega-3-acid ethyl esters) Capsules

Rx only

120 Capsules

Reliant PHARMACEUTICALS, INC.

Each capsule contains 1 gram omega-3-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.

Each capsule provides:
Eicosapentaenoic acid (EPA) ethyl ester: 465 mg
Docosahexaenoic acid (DHA) ethyl ester: 375 mg

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].
Do not freeze.

See package insert for complete prescribing information.

Manufactured for:
Reliant Pharmaceuticals, Inc.
Liberty Corner, NJ 07938
by:
Cardinal Health
St. Petersburg, FL 33716

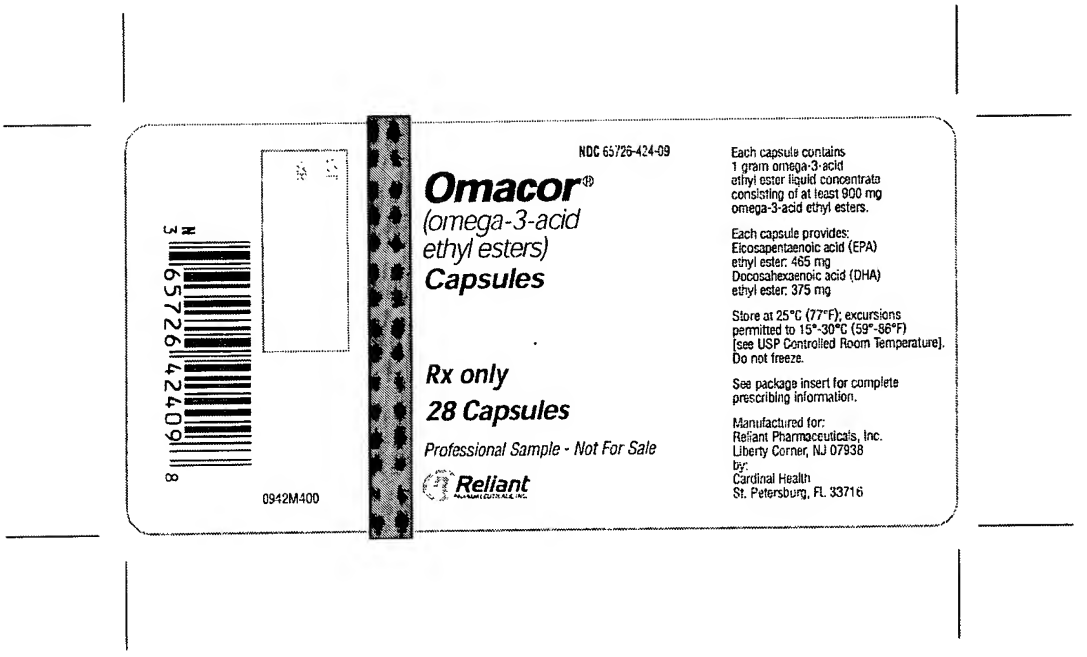
Black

Pantone Violet

PMS 1245

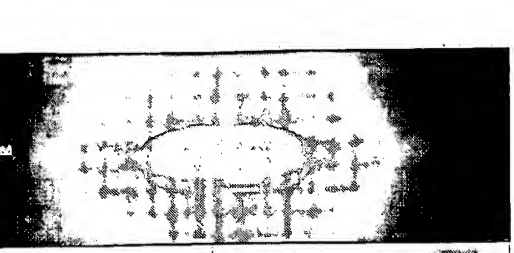
Non-varnish area inside

Label Size: 4.3" x 2.125"



OMACOR®
Omega-3-acid ethyl esters

Proven. Potent. Pure.™



ATTENTION: POTENTIAL DISPENSING ERRORS

OMACOR and AMICAR® (aminocaproic acid) Tablets.
Click here for more information.

Prescription OMACOR® (omega-3-acid ethyl esters) vs. dietary supplement omega-3

There are differences between a prescription medication and a dietary supplement. But what are they?

What exactly is a prescription medication?
A prescription medication is a drug that has passed the US Food and Drug Administration's (FDA's) rigorous review and approval process to ensure its safety and effectiveness. The FDA process includes a review of the manufacturer's clinical trials, claims that the drug is safe and effective for the condition that it claims to benefit, and its production plant, so that the drug created has the approved standards for consistency and purity.

OMACOR® (omega-3-acid ethyl esters) is a FDA-approved prescription medication.

What is a dietary supplement?
Unlike prescription medications, dietary supplements are foods, not drugs, and do not undergo rigorous FDA reviews for safety and effectiveness. Therefore, dietary supplements are not regulated as prescription medications, like OMACOR. Mandated manufacturing standards are less stringent for dietary supplements than they are for medications.

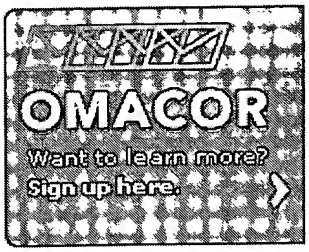
Tests by the United States Pharmacopeia (USP) have "shown that contents of many supplements sold in retail stores don't match the label and that some supplements contain significantly less or more than the claimed amount of key ingredients."

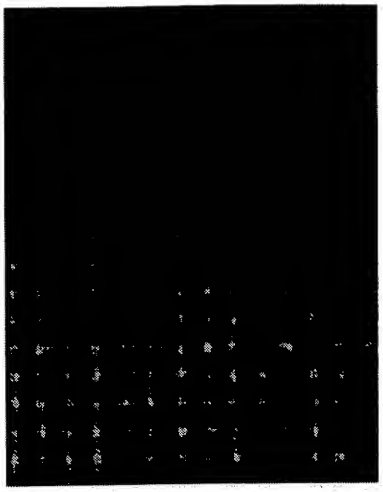
The FDA has not approved nonprescription, dietary supplement omega-3 for the treatment of any specific disease, like very high triglycerides.

- By prescribing OMACOR® (omega-3-acid ethyl esters), a prescription omega-3, your doctor is giving you a concentrated and reliable omega-3. Each OMACOR capsule contains 90% omega-3 acids (84% EPA/DHA*). Nonprescription omega-3 dietary supplements typically contain only 13%-63% EPA/DHA.*
- OMACOR is naturally derived through a unique, patented process that creates a highly concentrated, highly purified prescription medicine.
- The unique manufacturing process for OMACOR helps to eliminate concerns about mercury and other pollutants from

PRINTABLE DOCTOR DISCUSSION GUIDE

Let this free guide assist in your discussion about triglycerides, omega-3, and heart health with your doctor.
> Print Now





the environment.

*Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the effective natural ingredients of OMACOR.

Next Steps:

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Important Safety Information

Do not take OMACOR if you are allergic to any of the ingredients in OMACOR. OMACOR should be used with caution in people allergic to fish. OMACOR has not been studied in children under 18 years of age.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. OMACOR and other medicines may affect each other, causing side effects. Especially tell your healthcare provider if you take blood thinners. If you take both OMACOR and a blood thinner, you and your healthcare provider should be watchful for certain side effects, like bruising easily.

Tell your healthcare provider if you have liver problems or if you are pregnant, are trying to become pregnant, or are breast-feeding.

OMACOR is an addition to diet to help reduce very high (≥500 mg/dL) triglyceride (TG) levels in adult patients. Some possible side effects of OMACOR include burping, infection, flu symptoms, upset stomach, skin rash, and a change in your sense of taste.

Please see full

FDA News

FOR IMMEDIATE RELEASE
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September 8, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Announces Qualified Health Claims for Omega-3 Fatty Acids

The Food and Drug Administration (FDA) today announced the availability of a qualified health claim for reduced risk of coronary heart disease (CHD) on conventional foods that contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids.

Typically, EPA and DHA omega-3 fatty acids are contained in oily fish, such as salmon, lake trout, tuna and herring. These fatty acids are not essential to the diet; however, scientific evidence indicates that these fatty acids may be beneficial in reducing CHD.

"Coronary heart disease is a significant health problem that causes 500,000 deaths annually in the United States," said Dr. Lester M. Crawford, Acting FDA Commissioner. "This new qualified health claim for omega-3 fatty acids should help consumers as they work to improve their health by identifying foods that contain these important compounds."

A qualified health claim on a conventional food must be supported by credible scientific evidence. Based on a systematic evaluation of the available scientific data, as outlined in FDA's "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements", FDA is announcing a qualified health claim for EPA and DHA omega-3 fatty acids. While this research is not conclusive, the FDA intends to exercise its enforcement discretion with respect to the following qualified health claim:

"*Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of [name of food] provides [x] grams of EPA and DHA omega-3 fatty acids. [See nutrition information for total fat, saturated fat and cholesterol content.]*

In 2000, FDA announced a similar qualified health claim for dietary supplements containing EPA and DHA omega-3 fatty acids and the reduced risk of CHD. FDA recommends that consumers not exceed more

than a total of 3 grams per day of EPA and DHA omega-3 fatty acids, with no more than 2 grams per day from a dietary supplement.

The EPA and DHA omega-3 fatty acid qualified health claim is the second qualified health claim that FDA has announced for conventional food. For additional information about QHC visit: http://www.cfsan.fda.gov/~dms/lab-qhc.html.

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FDA Letter to Emord & Associates Responding to Omega-3 Health Claim Petition
FDA Letter to Hogan & Hartson Responding to Omega-3 Health Claim Petition
Petitions - Docket No. 2003Q-0401
